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Brief Articles

Reduced-Intensity Conditioning Hematopoietic Cell Transplantation Is an Effective Treatment for Patients with SLAM-Associated Protein Deficiency/X-linked Lymphoproliferative Disease Type 1

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A B S T R A C T

X-linked lymphoproliferative disease type 1 (XLP1) is a rare immune deficiency caused by mutations in *SH2D1A*. Allogeneic hematopoietic cell transplantation (HCT) is often performed because of the morbidity and mortality associated with XLP1. There is limited experience using reduced-intensity conditioning (RIC) regimens for these patients. Here we report our 8-year single-center experience. Sixteen consecutive patients diagnosed with XLP1 underwent allogeneic HCT between 2006 and 2013 after a RIC regimen consisting of alemtuzumab, fludarabine, and melphalan. Patient phenotypes included hemophagocytic lymphohistiocytosis (HLH) after Epstein-Barr virus (n = 5) or human herpesvirus 6 (n = 1), macrophage activation syndrome (n = 1), interstitial pneumonitis and encephalitis (n = 1), B cell lymphoma (n = 8), and hypogammaglobulinemia (n = 2). One patient was asymptomatic. Fourteen of 16 patients received 8/8 HLA-matched unrelated or related bone marrow grafts, whereas 2 patients received mismatched unrelated grafts. Acute graft-versus-host disease (GVHD) prophylaxis consisted of methylprednisolone and cyclosporine in all but 1 patient, who additionally received methotrexate. All patients had hematopoietic recovery. There were no cases of hepatic veno-occlusive disease or pulmonary hemorrhage. One patient (6%) developed acute GVHD and later also developed chronic GVHD (6%). Five patients (31%) developed mixed chimerism. Only 1 patient with mixed chimerism (6%) experienced a decline of donor chimerism to less than 50% but returned to full donor chimerism after infusion of donor lymphocytes and a $CD34^+$ selected stem cell boost. Infectious complications were frequent, particularly viral reactivation. One-year survival estimated by Kaplan-Meier analysis was 80%, with long-term survival estimated at 71%. Survival was similar for patients with or without a history of HLH (86% versus 75%, respectively, $P = .70$). There were no occurrences of lymphoma or HLH after HCT. RIC HCT with alemtuzumab, fludarabine, and melphalan is an effective treatment for patients with XLP1, offering good survival rates regardless of prior disease manifestations, including HLH.

INTRODUCTION

X-linked lymphoproliferative disease type 1 (XLP1) is a rare primary immune deficiency caused by mutations in the *SH2D1A* gene, which encodes the SLAM-associated protein [1-3]. XLP1 is commonly characterized by fulminant Epstein-Barr virus (EBV) infection and/or hemophagocytic lymphohistiocytosis (HLH) after EBV infection as well as B cell lymphoma, hypogammaglobulinemia, aplastic anemia, and vasculitis [4-7].Allogeneic hematopoietic cell transplantation (HCT) is often performed to improve reported poor long-term survival.

Historically, most XLP patients have been transplanted with a variety of myeloablative conditioning regimens, containing either total body irradiation with cyclophosphamide or busulfan with cyclophosphamide. In 2005, Lankester et al. [8] summarized the reported cases to that time (n = 14). Patients were treated with total body irradiation–based or busulfan-based myeloablative conditioning regimens in all but 2 cases. Several regimen-related toxicities were observed, but 71% of patients survived. The authors suggested caution with consideration of reduced-intensity conditioning (RIC) regimens, because 1 patient included in their review had died

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of progressive disease after a RIC regimen consisting of fludarabine, melphalan, and antithymocyte globulin [8].

Since then, increasing numbers of reports have become available regarding the use of RIC for XLP1. Experiences in Europe and Japan suggest that survival rates after RIC and myeloablative conditioning are similar [6,7]. In the largest series, Booth et al. [7] retrospectively reported the transplant outcomes for 43 patients transplanted at 22 centers. Patients transplanted with myeloablative conditioning or RIC regimens experienced similar survival rates of 82.9% and 78.9%, respectively. However, the authors noted a poor survival of only 50% among patients with a history of HLH before HCT, without an obvious impact of conditioning regimen. This is in contrast to experience with familial HLH, where RIC has been shown to greatly improve patient outcomes [9-11]. Interestingly, Booth et al. also noted 100% survival of patients without a history of HLH, which is unlikely to translate to all patients with XLP1 who lack a history of HLH. To gain additional perspective regarding the outcomes of patients with XLP1 undergoing RIC HCT, we report here a retrospective review of our single-center experience with 16 consecutive patients with XLP1 treated with a RIC regimen consisting of alemtuzumab, fludarabine, and melphalan.

METHODS

Patients and Transplant Procedures

Sixteen consecutive patients diagnosed with XLP1 were transplanted at our center between 2006 and 2013 using a RIC regimen consisting of alemtuzumab, fludarabine, and melphalan. Patients 1, 2, 4 to 9, 11, and 13 to 15 were also reported previously by Marsh et al. [12]. Conditioning regimens used in this series have been described in Cooper et al. [10], Shenoy et al. [13], and Marsh et al. [12], and dosing of alemtuzumab was modified over the duration of this report. Alemtuzumab was given either as a dose escalation schedule of 3 mg/10 mg/15 mg/20 mg or a cumulative 1-mg/kg dose beginning on day −14, −12, −11, or −9, except in 1 patient who, after starting alemtuzumab, developed acute renal insufficiency due to AmBisome (Gilead Sciences, Inc., San Dimas, CA), and the preparative regimen was temporarily halted. After 3 weeks the preparative regimen was again begun in this patient, and the patient received doses of 10 and 20 mg on days −12 and −11. All patients received fludarabine 150 mg/m^2 divided over days −8 to −4 or −7 to −3, and melphalan 140 mg/m^2 on day −3 or −2. Graft characteristics are shown in Table 1.

Acute graft-versus-host disease (GVHD) prophylaxis consisted of methylprednisolone 1 to 2 mg/kg and cyclosporine (to maintain goal levels 200 to 350 ng/mL). One patient additionally received methotrexate on days +1, +3, and +6. Engraftment studies were done using either XY fluorescence in situ hybridization in the case of sex mismatched donor or variable number of tandem repeat analysis in the case of same sex donor in the clinical genetics laboratory at Cincinnati Children's Hospital.

Whole blood chimerism studies were performed at the discretion of the primary physician and as clinically indicated and were initially performed twice weekly, weekly, or biweekly. Mixed chimerism was defined as whole blood donor chimerism of less than 95% on 2 or more occasions.

All patients received intravenous immunoglobulin replacement, antifungal prophylaxis, and anti–*Pneumocystis* (*carinii*) *jiroveci* prophylaxis per standard institutional practice. In patients with serologic evidence of prior herpes simplex virus or cytomegalovirus (CMV) or receiving a graft from a donor with serologic evidence of prior CMV, anti-CMV prophylaxis was also administered.

Outcomes and Survival Analyses

We retrospectively reviewed the medical records and recorded toxicities such as hepatic veno-occlusive disease or pulmonary hemorrhage, acute or chronic GVHD, and infectious complications. We reviewed charts for the date of last follow-up or death and the cause of death if applicable. Survival was estimated by generating Kaplan-Meier survival curves using XLSTAT (Addinsoft, Paris, France). Groups were compared using the log-rank test.

RESULTS

Patients and Transplant Procedures

Sixteen patients were diagnosed with XLP1 after flow cytometric and/or genetic testing (Table 1). Patient phenotypes included 1 or more of the following: a history of HLH after EBV (n = 5) or human herpesvirus 6 (n = 1), HLH-like hyperinflammatory presentations including macrophage activation syndrome (n = 1) and interstitial pneumonitis and encephalitis (n = 1), B cell lymphoma (n = 8), and hypogammaglobulinemia (n = 2). One patient was asymptomatic (diagnosed due to family history). HLH and lymphoma treatment details are shown in Table 1. One patient (patient 4) had active HLH at the start of the conditioning regimen, as defined by the presence of fever, pancytopenia, ferritin >500 ng/mL, elevated soluble IL-2 receptor alpha, and hemophagocytosis on bone marrow examination during the 2 weeks preceding the start of conditioning. All patients with a history of lymphoma were in complete remission at the time of transplantation.

Patients were transplanted after RIC consisting of alemtuzumab, fludarabine, and melphalan, as detailed in Methods. Graft characteristics are summarized in Table 2. Most patients (14/16) received 8/8 HLA-matched unrelated or related bone marrow grafts, whereas 2 patients received either 7/8 or 6/8 HLA-matched bone marrow grafts.

Engraftment and Chimerism

All patients had hematopoietic recovery, with neutrophil recovery between days 9 and 15 after HCT. Five patients developed mixed chimerism (31%) at a median of 99 days after HCT (range, 67 to 117). Because of the small size of the cohort, we were unable to meaningfully analyze variables that may have impacted the incidence of mixed chimerism, such as timing and dose of alemtuzumab, and history of lymphoma therapies. One patient maintained stable whole blood donor chimerism greater than 90% at last follow-up 2 years after HCT. Three patients developed stable mixed chimerism with donor contribution to hematopoiesis above 70% at last follow-up (median follow-up, 868 days; range, 188 to 2393 days) and did not receive any additional hematopoietic cell products. Whole blood donor chimerism declined to a minimum of 32% 167 days after HCT in a fifth patient. This patient received 12 serial donor lymphocyte infusions, beginning 112 days after HCT, and a CD34$^+$ selected stem cell boost 200 days after HCT. Whole blood donor chimerism returned to 95% 300 days after HCT, and he remains with full donor chimerism at last follow-up (1406 days after HCT).

Acute Toxicities

There were no occurrences of hepatic veno-occlusive disease or pulmonary hemorrhage.

Acute and Chronic GVHD

One patient (6%) developed grade III acute GVHD involving the skin and gastrointestinal tract. No other patients developed acute GVHD. This same patient later developed chronic GVHD of the skin and oral cavity, which had resolved at last follow-up (944 days after HCT).

Infectious Complications after Transplantation

Infectious complications after transplantation were common. Nine patients developed adenovirus viremia at a median of 13 days after transplant (range, 7 to 110 days); all 9 received cidofovir. Three patients developed CMV viremia at a median of 7 days after HCT (range, 5 to 49 days), and 2 were treated with ganciclovir, foscarnet, and cytogam. One patient developed quantifiable EBV viremia after HCT and was treated with rituximab, whereas 2 other patients developed

Table 1
Patient Demographics

Patient	XLP Phenotype(s)	Age at Initial Presentation (yr)	Site and Stage* of Lymphoma	Previous HLH, Inflammatory, or Lymphoma† Treatment	*SH2D1A* Mutation	HLH or Lymphoma Disease Status at HCT	Lansky or Karnofsky Performance Status Score [14,15]
1	EBV HLH	1		Dex, Etop, IT, Alem, Ritux	295 C>T (Q99X)	Quiescent	20
2	EBV HLH	1		Dex, Etop, CSA, Alem, Ritux	Gross deletion including exon 1, and 346(+3)	Quiescent	80
3	EBV HLH	1		Dex, Etop, Ritux	95 G>C (R32T)	Quiescent	100
4	HHV6 HLH	2		Dex, Etop, IT, CSA	201(+3) a>g	Active	80
5‡	Asymptomatic	Asymptomatic		Not applicable	163 C>T (R55X)	Not applicable	100
6	Burkitt's lymphoma	3	Nasopharynx with cervical LAD stage II	ANHL01P1-group B (Cy, Vcr, Dox, MTX, ARA-c, Pr, Ritux)	Not available	Complete remission	100
7‡	Burkitt's lymphoma	3	Left cervical region and right kidney stage II	CCG-5961-group B4 (Cy, Vcr, Dox, MTX, ARA-c, Pr)	163 C>T (R55X)	Complete remission	90
8	EBV HLH	4		Dex, Etop, Ritux	Gross deletion including exons 1-4	Quiescent	90
9‡	Burkitt's lymphoma	6	Ascending colon, cecum and CNS stage IV	ANHL-01P1-group C (Cy, Vcr, Dox, Mtx, ARA-c, Etop, Pr, Ritux)	163 C>T (R55X)	Complete remission	100
10	Interstitial pneumonitis and encephalitis	7		Methylprednisolone	195_196 insT (A66fsX67)	Not applicable	80
11	EBV HLH, Hypogam	2		Dex, Etop, IT	125 G>A (C42Y)	Quiescent	100
12	Diffuse large B cell lymphoma, 2 occurrences, ages 6 yr and 9 yr	6	Abdominal, cervical and axillary LAD stage III Ascending colon and mesenteric LAD stage II	ANHL-01P1-group B (Cy, Vcr, Dox, MTX, ARA-c, Pr, Ritux) ANHL0121 (R-Ifo, Car, Etop)	117 C>T (G39G)	Complete remission	90
13	Large B cell lymphoma, 3 occurrences, ages 3 yr, 5 yr, and 9 yr; Hypogam	3	Large bowel mass stage III Perirectal mass stage II Right cervical LAD stage I	CCG-5961-group B3 (Cy, Vcr, Dox, MTX, ARA-c, Pr) CCG 5961- (Cy, ARA-c, Pr, Etop) CCG 5961- (Cy, ARA-c, Pr, Etop)	Gross deletion including exons 2-4	Complete remission	90
14	Large B cell lymphoma, macrophage activation syndrome	1	Left renal, paraspinal mass and BM stage IV	POG-9315 (Vcr, Dox, Pr, MTX, ARA-c, 6-MP) Methylpred-nisolone, CSA	Gross deletion including exons 1-4	Complete remission Quiescent	90
15	Burkitt's lymphoma, 2 occurrences, ages 5 yr and 15 yr	5	Lymph nodal mass near caecum stage II Abdominal mass stage III	CCG-5961-group A (Cy, Vcr, Dox, Pr) ANHL01P1-group B (Cy, Vcr, Dox, MTX, ARA-c, Pr, Ritux)	Gross deletion including exon 2	Complete remission	100
16	B cell lymphoma	9	Terminal ileum stage II	CCG-5961-group B (Cy, Vcr, Dox, MTX, ARA-c, Pr)	195_196 insT (A66fsX67)	Complete remission	100

Dex indicates dexamethasone; Etop, etoposide; IT, intrathecal hydrocortisone +/− methotrexate; Alem, alemtuzumab; Ritux, rituximab; CSA, cyclosporine; LAD, lymphadenopathy; Cy, cyclophosphamide; Vcr, vincristine; Dox, doxorubicin; MTX, methotrexate; ARA-c, cytarabine; Pr, prednis(ol)one; Hypogam, hypogammaglobulinemia; CNS, central nervous system; R-Ifo, rituximab plus ifosfamide; Car, carboplatin; BM, bone marrow; 6-MP, 6-mercaptopurine.

* Modified Murphy staging for childhood non-Hodgkin lymphoma.

† All patients were either enrolled or treated as per Children's Cancer Group (CCG-5961), Pediatric Oncology Group (POG-9315), and Children's Oncology Group (ANHL01P1 and ANHL0121) studies.

‡ Patients are siblings.

transient unquantifiable levels of EBV < 200 copies/μg of DNA. BK viremia occurred in 6 patients at a median of 46 days (range, 12 to 85 days) after transplant, with 2 experiencing hemorrhagic cystitis. Human herpesvirus 6 viremia occurred in 2 patients and varicella viremia in 1 patient. Respiratory syncytial virus and human metapneumovirus infections were observed in 1 patient each. Human metapneumovirus was associated with pneumonitis, respiratory failure, acute respiratory distress syndrome, and pulmonary thrombotic microangiopathy, and its contribution to pathogenesis is unclear. Three episodes each of gram-negative or gram-positive sepsis occurred. One patient developed *P.* (*carinii*) *jiroveci* pneumonia associated with respiratory failure (despite appropriate prophylaxis). Candidemia occurred in 1 patient, and 1 patient developed a presumed fungal infection of the central nervous system.

Survival

Four of 16 patients died. Three patients died due to infectious complications related to HCT, including human

Table 2
Transplant Information

Patient	Age at HCT (yr)	Donor Match	Donor Relation	Stem Cell Source	Donor CMV	Patient CMV	Donor EBV	Patient EBV	GVHD Prophylaxis	Nucleated Cell Dose ($\times 10^8$/kg)
1	1.8	8/8	Sibling	Marrow	–	+ (IVIG)*	+	+†	Cyclosporine and methylprednisolone	12.8
2	1.8	6/8	Unrelated	Marrow	+	+ (IVIG)	+	+†	Cyclosporine and methylprednisolone	7
3	2.0	8/8	Unrelated	Marrow	–	–	+	+†	Cyclosporine and methylprednisolone	5.5
4	2.7	8/8	Unrelated	Marrow	+	+ (IVIG)	+	+ (IVIG)	Cyclosporine and methylprednisolone	4.7
5‡	3.4	8/8	Sibling	Marrow	–	–	–	–	Cyclosporine and methylprednisolone	10.7
6	3.5	8/8	Sibling	Marrow	+	+ (IVIG)	+	+ (IVIG)	Cyclosporine and methylprednisolone	11.5
7‡	5.1	8/8	Unrelated	Marrow	–	+ (IVIG)	+	+ (IVIG)	Cyclosporine and methylprednisolone	11.2
8	5.4	8/8	Sibling	Marrow	–	+ (IVIG)	+	+†	Cyclosporine and methylprednisolone	7.8
9‡	6.8	8/8	Sibling	Marrow	–	+ (IVIG)	–	+ (IVIG)	Cyclosporine and methylprednisolone	10
10	8.0	8/8	Unrelated	Marrow	–	+ (IVIG)	–	+ (IVIG)	Cyclosporine and methylprednisolone	3.7
11	10.2	8/8	Unrelated	Marrow	+	+ (IVIG)	+	+†	Cyclosporine and methylprednisolone	2.7
12	10.4	8/8	Sibling	Marrow	–	+ (IVIG)	+	+ (IVIG)	Cyclosporine and methylprednisolone	6.4
13	11.8	8/8	Unrelated	Marrow	–	+ (IVIG)	+	+ (IVIG)	Cyclosporine and methylprednisolone, methotrexate +1, 3, and 6	5.7
14	12.6	7/8	Unrelated	Marrow	+	+ (IVIG)	+	+ (IVIG)	Cyclosporine and methylprednisolone	4.1
15	16.0	8/8	Sibling	Marrow	–	+ (IVIG)	–	+ (IVIG)	Cyclosporine and methylprednisolone	7.1
16	17.7	8/8	Unrelated	Marrow	–	+	+	–	Cyclosporine and methylprednisolone	1.5

IVIG indicates intravenous immune globulin.
* Patients with positive serologic testing while receiving IVIG replacement and without positive IgM or PCR testing indicated by (IVIG).
† Positive for EBV by PCR and/or positive IgM antibody.
‡ Patients are siblings.

metapneumovirus with pneumonitis, respiratory failure, acute respiratory distress syndrome and pulmonary thrombotic microangiopathy, *P.* (*carinii*) *jiroveci*, and adenovirus infection together with central nervous system fungal infection. A fourth patient died more than 2 years after HCT due to complications of a multivisceral transplant, which was undertaken due to short-gut syndrome that preceded the HCT and was the result of necrotizing enterocolitis. The estimated 1-year survival of patients was 80% with no difference observed between patients with or without a history of HLH, 86% versus 75%, respectively ($P = .70$) (Figure 1A). Long-term survival was estimated at 71% (Figure 1B).

DISCUSSION

Our experience suggests that alemtuzumab, fludarabine, and melphalan RIC HCT is an effective preparative regimen for patients with XLP1 undergoing allogeneic transplantation. Overall, patient survival appears to be similar to rates reported in patients who received a variety of different conditioning regimens in the literature, as the 1-year and long-term survival in our cohort were 80% and 71%, respectively, compared with reports of 71% to 92% [6-8]. Importantly, we observed that survival appears to be equally good for patients with and without a history of HLH, although this observation is limited by the retrospective nature of this study and the small number of patients. This is in contrast to the data reported by Booth et al. [7], noting poorer outcomes for patients with a history of HLH compared with their observation of 100% survival of patients without a history of HLH. We previously noted that RIC HCT can as much as double survival of patients with HLH due to genetic causes other than mutations in *SH2D1A* [9]. Coupled with this experience, the outcomes presented here for patients with XLP1 suggest that RIC HCT should especially be considered for patients with XLP1 and a history of HLH. Our experience also illustrates that patients without a history of HLH are prone to transplant-related mortality, and a lack of prior HLH does not necessarily portend survival.

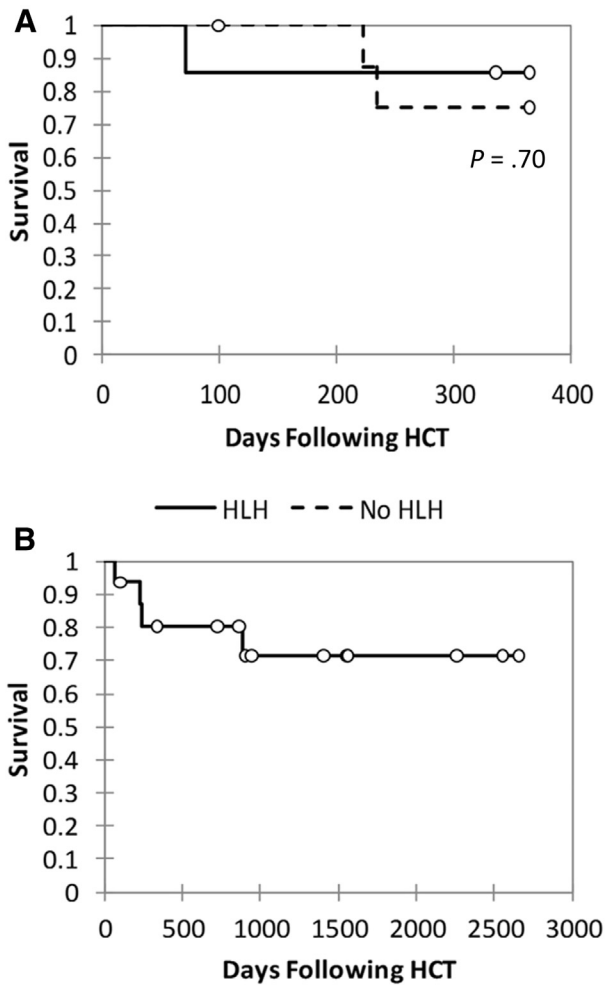

Figure 1. (A) One-year survival of patients with or without a history of HLH. (B) Long-term survival of patients after allogeneic RIC HCT.

Of note, infectious complications were common in our series and contributed to deaths in all but 1 of the children who died. As reported previously, adenovirus viremia was especially common after RIC HCT, occurring in half of patients, likely as a result of the inclusion of alemtuzumab in the conditioning regimen. Care should be taken to aggressively monitor patients for viral reactivations in patients receiving alemtuzumab-containing RIC HCT regimens, and treatment with antiviral therapies such as ganciclovir, foscarnet, cidofovir, brincidofovir, or other treatments should be considered early for patients with reactivation to prevent progression to disease, along with continuation or initiation of standard measures such as intravenous immunoglobulin replacement and cytomegalovirus immune globulin intravenous when appropriate.

Thirty-three percent of patients in this series developed mixed chimerism, and close monitoring as often as once a week is helpful to allow early intervention with donor lymphocyte infusions in cases with marked drops in donor chimerism. In our series, only 1 patient (6%) experienced a decline of donor contribution to hematopoiesis to less than 50% and received intervention with donor lymphocyte infusions and $CD34^+$ selected stem cell boost with good effect. This rate of mixed chimerism appears to be less than that previously reported for patients with HLH and related disorders, including XLP [12]. It is possible that this difference reflects a change in our practice to dose alemtuzumab at 1 mg/kg beginning on day −14, which 44% of patients in this series received, in an effort to decrease the incidence of mixed chimerism as we reported previously [12]. It may also reflect the prior chemotherapy received by 8 patients for treatment of 1 or more episodes of lymphoma.

We conclude that RIC consisting of alemtuzumab, fludarabine, and melphalan is a feasible approach for patients with XLP1 and appears to result in good outcomes for most patients, with no relapses of HLH or lymphoma observed in this series. RIC should especially be considered for patients with XLP1 who have a history of HLH. The currently evolving availability of broad-spectrum antivirals and adjunctive therapies such as virus-specific cytotoxic T lymphocyte products will likely continue to further improve patient outcomes by successful prevention and treatment of common viral complications. Additionally, future modifications to RIC regimens to further decrease the incidence of mixed chimerism will likely reduce the need for additional hematopoietic cell products after HCT and simplify post-HCT care, which may lead to a more widespread use of this approach.

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